

CLAIMS

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What is claimed is:

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1. A method of inhibiting vascular hyperpermeability in an individual comprising the step of administering to said individual a compound that inhibits the cellular signaling function of KDR.

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2. The method of Claim 1 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.

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3. The method of Claim 1 wherein said cellular signaling function of KDR is stimulated by the binding of an activating ligand to the receptor portion of KDR.

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4. The method of Claim 3 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.
5. The method of Claim 1 wherein said inhibition of the cellular signaling function of KDR is a process selected from the group consisting of blocking the production of an activating ligand, modulating the binding of the activating ligand to the KDR tyrosine kinase receptor, disrupting the dimerization of the receptor, blocking KDR trans-phosphorylation, inhibiting the activity of the KDR tyrosine kinase, impairing the recruitment of intracellular substrates of KDR, and interrupting the downstream signaling initiated by the phosphorylation activity of the KDR tyrosine kinase.

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6. The method of Claim 5 wherein said inhibition of the cellular signaling function of KDR is selective for the KDR signaling function.

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7. The method of Claim 1 wherein said compound inhibits the catalytic kinase activity of said KDR.

8. The method of Claim 1 wherein said compound is an antagonist of KDR tyrosine kinase activation.

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9. The method of Claim 1 wherein said compound selectively inhibits the phosphorylation of KDR kinase substrates.

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10. The method of Claim 1 wherein said compound is selective for said KDR tyrosine kinase.

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11. The method of Claim 10 wherein said compound is selected from the group consisting of peptides, antibodies and organic molecules, wherein said compound binds to said KDR tyrosine kinase.

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12. The method of Claim 11 wherein the administration of said compound inhibits the formation of a disease state selected from the group consisting of macular edema, aphakic/pseudoaphakic cystoid macular edema, retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, tissue edema at sites of trauma and allergic inflammation, allergies, hypersensitive reactions, polyp edema at sites of chronic inflammation, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, inhalation burn injury, skin burns, blistering associated with sunburn, irritation or infection, erythema multiforme, edematous macules and other skin disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion,

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hypotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, and the administration of growth factors.

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13. The method of Claim 10 wherein adverse effects associated with an alteration in the cellular signaling function of tyrosine kinases other than KDR are avoided when said compound is administered.
- 10 14. The method of Claim 1 wherein said compound is selected from the group consisting of single-chain antibodies, KDR-specific ribozymes and anti-sense polynucleotides, wherein said compound is introduced or produced intracellularly thereby inhibiting the proper presentation of functional KDR tyrosine kinase.
- 15 15. The method of Claim 1 wherein said compound is administered in combination with a pharmaceutical agent selected from the group consisting of an anti-endemic steroid, a Ras inhibitor, anti-TNF agents, anti-IL1 agents, an antihistamine, a PAF-antagonist, a COX-1 inhibitor, a COX-2 inhibitor, a 20 NO synthase inhibitor, a nonsteroidal anti-inflammatory agent (NSAID), a PKC inhibitor and a PI₃ kinase inhibitor.
- 25 16. A method of inhibiting a physiological process or state in an individual, said physiological process or state selected from the group consisting of edema formation, diapedesis, extravasation, effusion, exudation, ascites formation, matrix deposition and vascular hypotension, wherein said inhibiting comprises the administration of a compound that inhibits the cellular signaling function of KDR.
- 30 17. The method of Claim 16 wherein said compound is selective for said KDR tyrosine kinase.
- 35 18. The method of Claim 17 wherein said compound is selected from the group consisting of peptides, antibodies and organic molecules, wherein said compound binds to said KDR tyrosine kinase.
19. The method of Claim 18 wherein the administration of said compound inhibits the formation of a disease state selected from the group consisting of macular edema, aphakic/pseudoaphakic cystoid macular edema,

5 retinoblastoma, ocular ischemia, ocular inflammatory disease or infection, choroidal melanoma, edematous side-effects induced by iron chelation therapy, pulmonary edema, myocardial infarction, rheumatoid diseases, anaphylaxis, tissue edema at sites of trauma and allergic inflammation, allergies, hypersensitive reactions, polyp edema at sites of chronic

10 inflammation, cerebral edema, brain tumor fluid-filled cysts, communicating hydrocephalus, carpal tunnel syndrome, organ damage resulting from a burn, inhalation burn injury, skin burns, blistering associated with sunburn, irritation or infection, erythema multiforme, edematous macules and other skin disorders, brain tumors, tumor effusions, lung or breast carcinomas, ascites, pleural effusions, pericardial effusions, high altitude "sickness", radioanaphylaxis, radiodermatitis, glaucoma, conjunctivitis, choroidal melanoma, adult respiratory distress syndrome, asthma, bronchitis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, menstrual swelling, menstrual cramps, stroke, head trauma, cerebral infarct or occlusion,

15 hypotension, ulcerations, sprains, fractures, effusions associated with synovitis, diabetic complications, hyperviscosity syndrome, liver cirrhosis, microalbuminuria, proteinuria, oliguria, electrolyte imbalance, nephrotic syndrome, exudates, fibroses, keloid, and the administration of growth factors.

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20. The method of Claim 16 wherein said compound inhibits the catalytic kinase activity of said KDR.

21. The method of Claim 16 wherein said compound is an antagonist of KDR tyrosine kinase activation.

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22. The method of Claim 16 wherein said compound selectively inhibits the phosphorylation of KDR kinase substrates.

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23. The method of Claim 16 wherein said compound is selective for said KDR tyrosine kinase.

- 5 24. The method of Claim 16 wherein said cellular signaling function of KDR is
stimulated by the binding of an activating ligand to the receptor portion of
KDR.
- 10 25. The method of Claim 24 wherein said compound is selective for said KDR
tyrosine kinase.
- 15 26. The method of Claim 16 wherein said compound is selected from the group
consisting of single-chain antibodies, KDR-specific ribozymes and anti-sense
polynucleotides, wherein said compound is introduced or produced
intracellularly thereby inhibiting the proper presentation of functional KDR
tyrosine kinase.
- 20 27. The method of Claim 16 wherein said inhibition of the cellular signaling
function of KDR is a process selected from the group consisting of blocking
the production of an activating ligand, modulating the binding of the
activating ligand to the KDR tyrosine kinase receptor, disrupting the
dimerization of the receptor, blocking KDR trans-phosphorylation, inhibiting
the activity of the KDR tyrosine kinase, impairing the recruitment of
intracellular substrates of KDR, and interrupting the downstream signaling
initiated by the phosphorylation activity of the KDR tyrosine kinase.
- 25 28. The method of Claim 16 wherein adverse effects associated with an
alteration in the cellular signaling function of tyrosine kinases other than
KDR are avoided when said compound is administered.
- 30 29. The method of Claim 16 wherein said compound is administered in
combination with a pharmaceutical agent selected from the group consisting
of an anti-endemic steroid, a Ras inhibitor, anti-TNF agents, anti-IL1 agents,
an antihistamine, a PAF-antagonist, a COX-1 inhibitor, a COX-2 inhibitor, a
NO synthase inhibitor, a nonsteroidal anti-inflammatory agent (NSAID), a
35 PKC inhibitor and a PI_3 kinase inhibitor.